Remarks:

Applicant has amended claim 2 to direct it to the embodiment, wherein two single stranded nucleic acids are added to the original template at one end and a loop is added to the other end to make a hairpin structure that is open at one end and closed at the other end. The Applicant has further amended claim 2 to clarify that one of the single stranded nucleic acid is added to the 5' end of the upper strand of the double-stranded template nucleic acid and the other single stranded nucleic acid is added to the 3' end of the lower strand of the double-stranded template nucleic acid. Support for the amendments can be found throughout the specification, and for example at Figures 1, 3, 4 and 5. Accordingly, no new matter has been introduced by the amendments and their entry is respectfully requested.

Applicant has amended claim 6 to make explicit that which was implicit, namely, to incorporate the steps for the method for making the first hairpin nucleic acid structure to step (a). Claim 6 has been further amended to make explicit that which was implicit, namely that the step (b) refers to amplification of the first hairpin structure of step (a) and that the step (c) relates to creation of second hairpin structures wherein any nucleic acid that was amplified in step (b) that has polymerase introduced errors will result in a gap in the otherwise complementary structure of the hairpin, i.e. has a mismatch. Support for these amendments can be found throughout the specification and claims as originally filed, for example, claim 2, and par. [006], and [0012]. Accordingly, no new matter is introduced by the virtue of these amendments and their entry is respectfully requested.

Applicant has also amended claim 8 to make explicit that which was implicit, namely that the term mismatch referred to in the claim refers to the possible gaps in the second hairpin structure that are a result of an error by a polymerase enzyme during the amplification of the first hairpin structure. Support for these amendments can be found throughout the specification and claims as originally filed, for example, claim 2, and par. [006], and [0012]. Accordingly, no new matter is introduced by the virtue of these amendments and their entry is respectfully requested.

Applicant has cancelled claims 11, 13, and 14 without prejudice.

Applicant has added claim 35 to an embodiment, that was originally present in claim 1.

Applicant has added claims 36 and 37 to the embodiments that were originally present in claim 14, namely, claim 36 is directed to an embodiment, wherein the PCR of step (b) of claim 6

is performed using a regular PCR, i.e. PCR wherein the concentration of the primers is substantially equal. Claim 37 is directed to an embodiment, wherein the PCR of step (b) of claim 6 is performed using an asymmetric PCR, i.e. the concentration of one primer is substantially higher than the concentration of the other primer. As such, the new claims are supported by the claims and specification as originally filed, and do not introduce new matter and their entry is respectfully requested.

Turning now to the specific rejections.

Claims 2, and 6-17 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner contended that claim 2 was indefinite because the second option as set forth in the claim under "(2)" did not indicate an upper and lower single-stranded regions as set forth in the first option (1). To clarify the claim, the Applicant has cancelled the option 2 from claim 2, and present a claim directed to option 2 as a new claim 35. Accordingly, the Applicant respectfully submits that claim 2 and the new claim 35 now comply with 35 U.S.C. §112, second paragraph.

The Examiner further contended that claims 2, and 6-17 were confusing because she could not determine what was encompassed by the phrase "a hairpin DNA structure." The Applicant respectfully submits that the term "hairpin structure" should be well recognized within the art. Such a structure refers to a "stem and loop" structure, or a nucleic acid that has a region that forms a complementary double-stranded nucleic acid structure in the middle and a non-complementary structure loop at connecting the complementary regions. However, the Applicant has amended the claims to further clarify that the first hairpin structure is a structure wherein the double-stranded template nucleic acid forms the double-stranded part of a hairpin and the added single-stranded non-complementary structures at the ends of the template nucleic acid form the non-complementary end loop (claim 2) or loops (claim 35). Claim 6 has been further amended to refer to first and second hairpin structures because in step (a) one forms a first hairpin structure that is amplified and in step (b) the amplified hairpin structure is denatured and allowed to form a second hairpin structure. In view of the above, the Applicant respectfully submits that all the claims now comply with 35 U.S.C. §112, second paragraph, with respect to the term "hairpin structure."

The Examiner rejected claims 6-17 as failing to comply with 35 U.S.C. §112, second paragraph, as omitting essential elements.

The Applicant has amended claim 6 to include into step (a) the method steps to form the first hairpin structure as set forth, *supra*. Accordingly, the Applicant respectfully submits that the claims now clearly set forth all the elements, and comply with 35 U.S.C. §112, second paragraph.

Claims 6 and 14 were further rejected because of lack of antecedent basis for the phrases upper and lower single stranded regions. The Applicant has amended claim 6, as described, *supra*. As such, the Applicant respectfully submits that all the terms now have proper antecedent basis. Claim 14 has been cancelled.

Claim 8 was rejected based on insufficient antecedent basis for the phrase "double stranded region." The Applicant has amended claim 6 as set forth and described, *supra*. Specifically, claim 6 now specifies that the hairpin structure has a double-stranded region and a single stranded loop. Accordingly, the Applicant respectfully submits that all the terms in claim 8 now have proper antecedent basis.

The Examiner further contended that claim 11 was unclear because it recited terms "matched structure" and "mismatched structure." The Applicant has cancelled claim 11 without prejudice. As such, the rejection has been rendered moot.

The Examiner also contended that claim 13 was confusing because allegedly it was not clear how claim 13 further limits claim 12. While the Applicant disagrees, to expedite prosecution, the Applicant has cancelled the embodiment of claim 13 without prejudice.

In view of the above, the Applicant respectfully submits that all the claims comply with 35 U.S.C. §112, second paragraph, and requests that the rejections based on this section of the law should be withdrawn.

The Examiner rejected claim 2 as allegedly anticipated under 35 U.S.C. §102(b) by U.S. Patent No. 6,235,502 to Weissman.

Applicant respectfully disagrees and submits that the rejection should be withdrawn for the following reasons.

The method of Weissman is not directed to a method to amplify a double-stranded portion of the template nucleic acid as one linear template using primers that attach to a portion

of a single stranded nucleic acid structure attached to the 5' end of the double-stranded template and also to the single stranded nucleic acid structure attached to the 3' end of the double-stranded template. Weissman specifically states that "[t]he 3'OH at the nick serves as **a primer** for DNA synthesis (col. 3, lines 17-18, emphasis added). Because Weissman amplifies the template only using one primer (see, Id., and, e.g. Figures 1C, 1D and 1E) only one strand of the template is amplified. This is because Weissman is directed to an entirely different purpose, namely, amplifying templates **to allow isolation of nucleic acids via selective circularization** of the template (see, e.g., col. 3, lines 23-26). Thus, in the method of Weissman, one uses only one primer, **not first and a second primer** as required by the present method. Also, Weissman converts DNA fragments into a form that can be utilized as RCA templates by ligation of hairpin forming adapters to the end of the fragments "wherein the **adapters have 3' and 5' ends that are complementary to each other** such that they form stem and loop structures" (col. 4, lines 57-62, emphasis added). In the present method, the adapters must remain single-stranded. Accordingly, Weissman cannot anticipate claim 2 and will also not apply to claim 35.

Claim 2 requires use of two primers that result in amplification of both the upper and the lower strand in one single linear template, wherein the other strand of the linear product is complementary to the original upper and lower strand of the template.

Further, with respect to the amended claim 2, Weissman also does not describe a hairpin structure that has two single stranded nucleic acids attached to one end of the double-stranded template and wherein the double-stranded region is connected at only one end.

In view of the above and the amendments to claim 2, the Applicant respectfully submits that claim 2, cannot be anticipated by Weissman. Thus, rejection of claim 2 under 35 U.S.C. §102(b) should be withdrawn.

Claim 2 was also rejected as allegedly being obvious under 35 U.S.C. §103(a) in light of U.S. Patent No. 5,470,724 to Ahern, in view of Liu et al.

Applicant respectfully disagrees and submits that the rejection should be withdrawn for the following reasons.

Similarly to Weissman, Ahern is also directed to a method wherein one only uses one primer. In col. 2, Ahern specifically states, that the "key advantage of BDA is that DNA amplification can be performed using only one primer" and that "[a]s a result, the DNA that is

amplified using BDA is not limited to a region of the DNA situated between two primers." (Emphasis added). This is contrary to the present method and completely contrary to the purpose of the present method. The **method of claim 2 requires that one must use two primers** that amplify a region between the primers, and that only the region between these two primers be amplified. Accordingly, Ahern does not teach a method wherein a double-stranded region is amplified using one primer that attaches to at least a portion of a single stranded nucleic acid attached to the 5' end of the upper strand of the template nucleic acid and another primer attaches to at least a portion of a single stranded nucleic acid attached to the 3' end of the lower strand and amplifying the region in between thereby resulting in a linear PCR product that encompasses both the upper and lower strands of the template as the new "upper strand" and its complementary strand as the new amplified lower strand.

Liu does not overcome this deficiency in Ahern. Liu only teaches truncation of DNA polymerase elongation using modified nucleotides incorporated into the template sequence. Moreover, also the method of Liu is directed to using a modified PCR. As described in the abstract "[t]runcated amplificatyion utilizes pairs of oligonucleotides and thermal cycling but is different from PCR. Truncated amplification amplifies non-exponentially with one or two chimeric oligonucleotides and produces truncated terminal products that are no more than three rounds of replication from the original template." This is vastly different approach to overcome the error problem associated with PCR amplification. What Liu teaches is that to solve the problem of PCR errors one should avoid using PCR and instead use the truncated amplification as they describe. There is nothing in Liu that would direct on skilled in the art to use two primers as claimed to supplement the method as described by Weissman.

Even assuming, *arguendo*, that the combination would teach all the elements, there would have been no motivation to combine these two references because neither Weissman nor Liu talk about amplifying a hairpin structure so that one ends up with a structure wherein both upper and lower strands of the template are present in one strand of the resulting linear nucleic acid and the other strand is complementary to this strand. Furthermore, Liu specifically teaches that one should avoid using PCR to increase fidelity of amplification reaction (see, e.g., p. 136, 1st col., under heading "TA versus PCR")

Accordingly, in view of the above and the amendments to claim 2, the Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) over Ahern in view of Liu be withdrawn.

Claims 6-17 were rejected as allegedly being obvious 35 U.S.C. §103(a) over Weissman in view of U.S. Patent No. 6,114,115 to Wagner.

Applicant respectfully disagrees and submits that the rejection should be withdrawn for the following reasons.

As already discussed above, Weissman does not teach use of two primers recognizing at least a portion of a single stranded region attached to the 5' end of an upper strand of a template nucleic acid and a second primer that recognizes at least a portion of a single-stranded region attached to the 3' end of the lower strand of a template to amplify a template so that the amplification between these primers results in a linear PCR product that comprises as one of its strands a copy of the original template and its complementary strand and as the other of its strands is a complementary of the above. Wagner does not overcome this deficiency. Wagner only describes one method for removing mismatch-containing duplex nucleic acids. There is nothing in the combination of these two references that teaches a method that requires generation of a first hairpin structure as taught in step (a) of claim 6, amplifying the structure with two primers to obtain plurality of linear PCR products and then using denaturation and rapid renaturation to form a second hairpin structures from the amplified linear PCR products to identify the PCR products that contain polymerase induced amplification errors.

Accordingly, in view of the claim amendments and the above, the Applicant respectfully submits that the rejection under 35 U.S.C. §103(a) over Weissman in view of Wagner be withdrawn.

Claims 6-17 were also rejected as allegedly being obvious 35 U.S.C. §103(a) over Ahern in view of Wagner.

Applicant respectfully disagrees and submits that the rejection should be withdrawn for the following reasons.

As discussed, *supra*, the invention as claimed is directed to a method wherein one creates a first hairpin structure, amplifies that first hairpin wherein the amplification results in linear PCR products. After amplification, one uses a second hairpin structure formation to allow

capture of errors introduced in the first amplification step. The combination of Wagner and Ahern fails to teach such a method.

Accordingly, in view of the claim amendments and the above, Applicant respectfully submits that the rejection under 35 U.S.C. §103(a) over Ahern in view of Wagner be withdrawn.

Claim 2 was further rejected as allegedly being obvious under 35 U.S.C. §103(a) over U.S. Patent Application Publication No. 2003/0108902 to Abarzua in vie of Liu.

Applicant respectfully disagrees and submits that the rejection should be withdrawn for the following reasons.

Like the method of Weissman discussed, *supra*, the method as described in Abarzua is also directed to using one primer with the idea of creating a circular template. This is contrary to the present method that requires the use of two primers to PCR amplify a template resulting in a linear PCR product.

As discussed, *supra*, Liu teaches one to avoid PCR altogether in favor of TA (truncated amplification) to overcome the problems associated with PCR fidelity. This is completely contrary to what the present claims are directed to, and certainly does not overcome the deficiencies in Abarzua, which teaches only creating circular templates.

Accordingly, Applicant respectfully submits that the rejection under 35 U.S.C. §103(a) over Abarzua in vie of Liu be withdrawn.

Claims 6-17 were rejected under 35 U.S.C. §103(a) over as allegedly being obvious over Abarzua in view of Wagner.

Applicant respectfully disagrees and submits that the rejection should be withdrawn for the following reasons.

As discussed above, the method of Abarzua is directed to formation of a single-stranded circular nucleic acids, not a double-stranded linear structure which is the result of the step (a) of claim 6. Wagner does not overcome this deficiency. Wagner does not teach creation of the first hairpin structure and the subsequent amplification with two primers to result in a linear double-stranded product either. Thus, the combination of these references cannot render the present claims obvious.

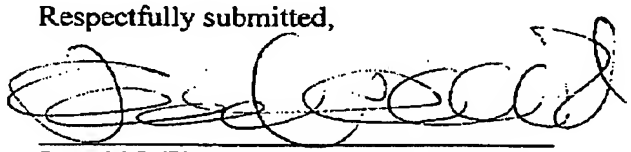
Accordingly, in view of the amendments to the claims and the arguments presented above and elsewhere in this Amendment, Applicant respectfully submits that the rejection under 35 U.S.C. §103(a) over Abarzua in vie of Wagner be withdrawn.

In view of the above, the Applicant respectfully submits that all the claims are in condition for allowance. Early and favorable consideration is respectfully solicited.

In the event that any additional fees are required, the PTO is authorized to charge Nixon Peabody LLP Deposit Account No.50-0850.

Respectfully submitted,

Date: June 22, 2007



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